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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,369	05/22/2001	Daniel Zagury	ZAGURY3A	9905

1444 7590 07/18/2003

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,369	ZAGURY ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the c ver sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1, 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Office Action

Status of the Claims

1. Claims 1-5 are pending in the instant application.

Information Disclosure Statement

2. The information disclosure statements filed 21 February, 2001, and 01 May, 2003, have been in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

3. Claims 1-4 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are incomplete for omitting essential positive methods steps, such omission amounting to a gap between the steps (refer to M.P.E.P. § 2173.05(q)). *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Bd. Pat. App. & Inter. 1986). For instance, the claimed methodology (claim 1) fails to provide any correlation between the markers being measured and disease progression. How do the anti-tat antibody titer, tat protein level, and p24 protein level correlate with disease progression? The treatment method is also deficient because it fails to provide any correlation between the various parameters being measured and the treatment outcome. Appropriate amendment of the claim language is required to incorporate the salient characteristics of the methodology.

35 U.S.C. § 112, First Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 2 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods for the determination of the prognosis of an HIV-infected individual by measuring the level of anti-Tat antibodies, Tat protein, or p24 antigen in the sera of said patients.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows: 1) The disclosure fails to provide a convincing correlation between the level of anti-Tat antibodies, Tat protein, or p24 antigen and the stage of disease progression. First, the disclosure fails to measure Tat antigen levels. Thus, the skilled artisan cannot reasonably ascertain if this is a meaningful marker. Second, while it was reported that there was a statistically significant difference between nonprogressors (NP) and fast progressors (NP-P) in terms of p24 antigen levels and anti-Tat antibody levels,

nevertheless, this correlation is extremely weak. The values for the Tat antibody measurements were 0.39 for nonprogressors and 0.32 for progressors. The values for p24 antigen were 21.22 and 29.55 in nonprogressors and progressors, respectively. These are weak correlations and the skilled artisan would be reluctant to employ them in a meaningful prognostic protocol.

2) The prior art clearly teaches that Tat antibody profiles are not predictive of clinical outcome in HIV-infected patients. Reiss *et al.* (1991) examined the role of anti-Tat antibodies in disease progression in a large cohort and reported (see Abstract, p. 165) that "**antibody profiles** to nef, rev, **tat,** and protease **did not contribute to the prediction of outcome of infection.**" Franchini *et al.* (1987) also examined the association of anti-Tat antibodies with disease progression and concluded (see Abstract, p. 437) that "**No significant difference in antibody prevalence** ... to the 3'*orf*, *sor*, and ***tat*-III proteins (approximately 50%) was observed with regard to stage of the disease.**" Krone *et al.* (1988) also examined this issue and reported (see Abstract, p. 261) that "**Because of the low antigenicity of HIV-tat, antibodies to this regulatory protein are not a reliable marker for either early HIV-1 infection or subsequent disease progression.**" Thus, the prior art clearly contradicts the assertions made by applicants.

3) The prior art teaches that Tat antigen levels are not predictive of clinical outcome in HIV-infected patients. This is not surprising considering the low antigenicity of Tat and its role in viral biology. As set forth *supra*, Krone *et al.* (1988) clearly demonstrate that Tat is not very antigenic in HIV-infected patients. Franchini *et al.* (1987) reported (see Abstract, p.437) that "**screening with** the newly identified 3'*orf*, *sor*, and **tat-III proteins as antigens would confer no further diagnostic advantage.**" Thus, the skilled artisan would not expect the measurement of Tat antigen levels to be a useful index for disease progression.

4) The prior art teaches that p24 antigen levels are not predictive of clinical outcome in HIV-infected patients. Donovan *et al.* (1996) examined the relevance of p24 antigen levels during AIDS-associated opportunistic infections and reported (see Abstract, p. 401) "**there was no consistent or significant change in p24 antigen levels** or CD4 cell counts **with either the onset of or recovery from an event.**" Pedersen *et al.* (1992) examined the significance of p24 antigenaemia in patients receiving zidovudine and acyclovir and observed (see Abstract, p. 821) that "**Disease progression occurred irrespective of whether p24-antigen levels declined during therapy. No association between p24-antigen responses to therapy and baseline disease stage, Karnofsky score or baseline CD4 count was detectable** ... Change in antigen level in response to antiviral therapy needs further investigation before it is used as a surrogate marker for clinical efficacy of antiviral therapy." Additional studies by Molina *et al.* (1994) also observed that "**None of these markers correlated with survival**" and that "Plasma viraemia and **ICD-p24 Ag**, while providing useful short-term markers of zidovudine antiviral activity *in vivo*, **do not correlate with disease progression in patients with advanced HIV infection.**" Finally, Lafeuillade *et al.* (1994) concluded (see Abstract, p. 1028) that "In fact, **p24 antigenemia was correlated with only biological markers of immune activation ... The measurement of anti-p24 antibodies did not appear discriminative in our staging.**" Thus, the skilled artisan would readily question the usefulness of p24 antigen measurements as a predictor of disease progression.

Therefore, when all the aforementioned factors are considered in toto, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

6. Claims 3-5 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods of treating HIV-infected individuals through the administration of a Tat vaccine or methodologies that are contingent upon the successful administration of a Tat vaccine.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any working embodiments demonstrating that HIV Tat vaccines are effective in combating HIV infection and disease progression. This is not surprising considering the state-of-the-art.

2) The state-of-the-art pertaining to HIV vaccine development is one of failure. Several factors have contributed to vaccine failure including a lack of understanding of the correlates of protective immunity, a lack of understanding of those antigens that can reasonably be expected to confer a protective or therapeutic immune response, the quasispecies nature of HIV infection which leads to frequent immune escape, and the lack of adequate animal models with which to assess vaccine efficacy (Letvin, 1998; Johnston, 2000; Burton and Moore, 1998; Lee, 1997). Thus, the

skilled artisan would not expect Tat-containing "vaccine" compositions to provide a protective or therapeutic immune response.

Accordingly, when all the aforementioned factors are considered in toto, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

7. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648**.

8. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

9. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (703) 308-1122 or (703) 308-4027, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

22 August, 2003